Bladder Tumor Antigen Stat Test in Non-Urothelial Malignant Urologic Conditions

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Abstract

Background: The bladder tumor antigen stat is a simple and fast one-step immunochromatographic assay for the detection of bladder tumor-associated antigen in urine.

Objectives: To evaluate the BTA stat in non-bladder cancer patients in order to identify the categories contributing to its low specificity.

Methods: A single voided urine sample was collected from 45 patients treated in the urology clinic for conditions not related to bladder cancer. Each urine sample was examined by the BTA stat test and cytology.

Results: The overall specificity of the BTA stat test was 44%, which was significantly lower than that of urine cytology, 90%. The false positive rates for the BTA stat test varied among the different clinical categories, being highest in cases of urinary tract calculi (90%), and benign prostatic hypertrophy (73%). Exclusion of these categories from data analysis improved BTA stat specificity to 66%.

Conclusions: Clinical categories contributing to low BTA stat specificity can be identified, and their exclusion improves the specificity of this test.

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Early diagnosis of bladder cancer allows the possibility of less invasive surgical treatment and higher 5 year survival rates for superficial tumors [1,2]. Cystoscopy is considered to be the golden standard for the diagnosis of bladder cancer. The diagnostic workup usually includes voided or wash-urine cytology. However, urine cytology carries some disadvantages: it is examiner-dependent, it has a relatively low sensitivity for low grade bladder tumors [3], it is time consuming, and its results are not available immediately. To circumvent these pitfalls, several urinary tumor markers were devised, and were found to be simple, objective and sensitive alternatives to urine cytology [4–7].

The bladder tumor antigen stat test, performed in a disposable kit, detects bladder tumor-associated antigen within 5 minutes of placing fresh untreated urine in the well. The antigen detected – human complement factor-4-related protein – was found *in vitro* to be produced by human bladder cancer but not by non-cancerous cell lines [8]. The BTA stat test was reported to have higher sensitivity but lower specificity when compared with urine cytology [4]. The low specificity of the BTA stat test was suggested to be related to certain urinary tract pathologic conditions not associated with urothelial cancer.

BTA = bladder tumor antigen

The aim of the present study was to evaluate BTA stat test results for those non-urothelial cancer cases in order to identify possible clinical categories whose exclusion will enable improved specificity of the BTA stat test.

Patients and Methods

The study was conducted in the Bnai Zion Medical Center, Haifa, Israel, between April 1997 and September 1999. Eligible for participation were patients without a history of bladder cancer. Patients in whom bladder cancer was diagnosed during the investigation were excluded.

The study included 45 patients treated in the urology clinic for urinary tract calculi (n=10), renal cell carcinoma (n=9) prostatic carcinoma (n=5), urinary tract infection (n=3), benign prostatic hypertrophy (n=11), stress urinary incontinence (n=4), hematuria of unknown origin (n=2), and indwelling urinary catheter (n=1). Males comprised 71% of the population and females 29%.

All subjects provided a single midstream or catheterized urine sample prior to cystoscopy. A portion of the sample was processed according to the instructions provided in the BTA stat test kit, and the remaining urine was sent for cytologic examination. This was done according to standard procedures, with the performer blinded to the BTA test results. Cystoscopy was performed only when justified by the clinical circumstances.

The BTA stat test is performed by placing five drops of fresh untreated urine in the well of the disposable kit. Mixing with antibody in the well, the urine passes to the test zone that contains fixed capture antibodies. In the presence of bladder tumor-associated antigen, a visible line appears in the test zone. Any intensity of this line indicates a positive test. If no antigen is present, no line appears. The control zone of the kit contains a fixed reagent that combines with the antibody to form a visible line unrelated to the presence of bladder tumor-associated antigen in the urine. Therefore, appearance of a line in the control zone of the kit indicates its correct usage. The results are read within 5 minutes of placing urine in the well.

Specificity was calculated overall and within each clinical category. False positive rate was calculated for each category by dividing the number of false positives (a) by the sum of false positives (a) and true negatives (b) (false positive rate =a/a+b).

Results

The overall and differential results for the BTA stat test, voided urine cytology and cystocopy are presented in Tables 1 and 2. The

Table 1. Overall results of the BTA stat test and cystoscopy

Patient group	No. of patients	Positive BTA stat test	BTA stat false positive rate (%)	Cystoscopy	
				Positive	Negative
Urinary tract calculi	10	9	90	–	7
Renal cell carcinoma	9	2	22	–	2
Prostatic carcinoma	5	1	20	–	3
Urinary tract infection	3	1	33	–	2
Benign prostatic hypertrophy	11	8	73	–	11
Hematuria of unknown origin	2	1	50	–	2
Stress urinary incontinence	4	2	50	–	1
Indwelling urinary catheter	1	1	100	–	1
Total	45	25		0	29

Table 2. Differential specificity for voided urine cytology

Patient group	Voided urine cytology specificity (%)
Urinary tract calculi	100
Renal cell carcinoma	100
Prostatic carcinoma	75
Urinary tract infection	100
Benign prostatic hypertrophy	87.5
Hematuria of unknown origin	100
Stress urinary incontinence	–
Indwelling urinary catheter	0
Total	90.5

BTA stat test was found to be negative in only 20 of the 45 cases evaluated, yielding a specificity of 44%. This value was lower than the specificity value for urine cytology, calculated to be as high as 90%.

The BTA stat test false positive rates for the different categories were: urinary tract calculi 90%, renal cell carcinoma 22%, prostatic cancer 20%, urinary tract infection 33%, benign prostatic hypertrophy 73%, hematuria of unknown origin 50%, stress urinary incontinence 50%, and indwelling urinary catheter 100%.

Discussion

While several possible markers for urinary bladder cancer are still under investigation [4–7], the clinical usage of the BTA stat test as such a marker was already evaluated in several studies [4,9]. Most authors report an advantage of the BTA stat test over voided urine cytology in terms of sensitivity, yet the specificity of the BTA stat test is consistently described as lower.

In order to identify factors contributing to this low specificity of the BTA stat test, a heterogeneous population of non-bladder cancer patients was investigated. Stratification according to the urologic disturbance revealed differential false positive rates. The highest false positive rate was recorded among patients with urinary tract calculi (90%), followed by the benign prostatic hypertrophy group (73%). BPH, as a separate group, was not previously found to interfere with the BTA stat test. The false positive rate in the renal and prostate cancer groups was similar (22% and 20%, respectively), suggesting possible unification of these groups into one – titled non-urothelial malignancies. The heterogenicity of such a group may lead to different results, such as BTA stat test specificity of only 17% for tumors other than bladder cancer [4]. The presence of mRNA for human complement factor-H-related proteins in cultured prostate and renal carcinoma cell lines [4] may possibly explain the false positive BTA stat results in these patients.

Due to the small size of the other clinical categories, we believe that, at this point, conclusions should be drawn only regarding those categories discussed above. Nevertheless, it seems that the first two categories, urinary tract calculi and BPH, which exhibited high false positive rates, should be considered as exclusion criteria for the clinical usage of the BTA stat test, while the moderate false positive rates of the non-urothelial malignancies permit this category to remain as a relative exclusion criterion. This is emphasized by eliminating urinary tract calculi and BPH from the data analysis, whereby the specificity of BTA stat test improved from 44% to 66%. In conclusion, clinical categories contributing to the low specificity of BTA stat test can be identified, and their exclusion from data analysis leads to improvement of the BTA stat test's specificity.

BPH = benign prostatic hypertrophy

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